D16 --90 (amended). A method for preparing a trimeric polypeptide complex which comprises (i) admixing three monomer polypeptides according to claim 68, (ii) effecting complex formation between said monomer polypeptides, and (iii) isolating the resulting trimeric polypeptide complex.--

Please amend claim 94 to recite the following:

D17 --94 (amended). A chimeric product comprising a trimeric polypeptide complex according to claim 68, wherein said product does not elicit an antigenic response in a human subject.--

Please amend claim 101 to recite the following:

D18 --101 (amended). The method according to claim 100 wherein the composition is administered by a route selected from the group consisting of the intravenous route, the intraarterial route, the transmembraneus route of the buccal, anal or vaginal tissue, intranasal route, the pulmonary route, the transdermal route, intramuscular, subcutaneous, intratechal, inoculation into tissue, or by an implant.--

REMARKS

Amendments do not Introduce New Matter

No new matter is introduced into the specification by way of these amendments. New claims 106 and 107 find support throughout the specification as originally filed. New claim 106 finds support in the specification as originally filed, for example, on page 6, last paragraph extending to page 7. New claim 107 finds support in the specification as originally filed, for example, on page 34, lines 8-13 and lines 20-23. New claims 108-111 and 126-130 find support in the specification as originally filed, for example, on page 17, the last paragraph extending to page 18, line 7, and on page 35, lines 25-26. New claim 112 finds support in the specification as originally filed, for example, on page 33, lines 18-20. New claims 113-117 find support in the specification as originally filed, for example, on page 17, first full paragraph. New claim 118 finds support in the specification as originally filed, for example, on page 14, lines 11-15 and Figure 2. New claim 119 finds support in the specification as originally filed, for example, on page 8, lines 12-13 and Figure 1. New claim 120 finds support in the specification as originally filed, for example, on page 8, lines 18-20 and Figure 1. New claim 121 finds support in the specification as originally filed, for example, Figure 1. New claims 122-123 find support in the specification as originally filed,

for example, on page 21, last full paragraph. New claims 124-125 find support in the specification as originally filed, for example, page 22, lines 8-15. New claims 131-132 and 134 find support in the specification as originally filed, for example, on page 22, lines 29-33. New claim 133 finds support in the specification as originally filed, for example, on page 18, last full paragraph.

Objections

Specification

Rejections under 35 U.S.C. § 132

The Examiner objected to the amendments filed March 1, 2002 and February 2, 2001, as allegedly introducing new matter into the specification. More specifically, the Examiner objected to the language "SEQ ID NO:40 and 41 are portions of a larger Tripa DNA sequence."

Applicants have removed the offending language from the specification by way of amendment herein. Accordingly, Applicants believe that they have fully addressed the Examiner's concerns. Therefore, Applicants respectfully request reconsideration and withdrawal of the new matter rejection under 35 U.S.C. § 132.

Claims

The Examiner objected to claim 101 as reciting the misspelled word "og", as well as reciting "the buccal" twice. Applicants appreciate the Examiner's attention to these errors. Applicants have amended the claims herein, and believe that they have fully addressed the Examiner's concerns.

Drawings

The Examiner objected to Figures 1, 3, 5, 7, and 17 in light of the respective description of each of these figures. Applicants have amended herein the descriptions of figures 1, 3, 5, 7 and 17 to address the Examiner's objections. Applicants believe that they have addressed the Examiner's concerns, and respectfully request reconsideration and withdrawal of the objections to Figures 1, 3, 5, 7 and 17.

Applicants further submit herewith proposed amendments to Figures 1, 2, 3, 5, 6, 7, 13, 15, 17 and 19 under 37 C.F.R. § 1.121. The proposed amendments to the figures are presented in red ink on a separate sheet for each respective figure, for approval by the

Examiner. Applicants respectfully request consideration of the proposed amendments to the Figures and notification of acceptance of the Figure amendments by the Examiner.

Rejections

Rejections under 35 U.S.C. § 112, 2nd Paragraph

The Examiner rejected claims 22-24, 76, 82, 84, 87-90 and 94 under 35 U.S.C. § 112, 2nd Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have either amended or cancelled the rejected claims under the claim amendments presented *supra*, and accordingly have addressed the Examiner's rejections. Applicants respectfully request reconsideration and withdrawal of the rejections of claims 22-24, 76, 82, 84, 87-90 and 94 under 35 U.S.C. § 112, 2nd Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 19, 68-77, 83, 86, 90 and 98 under 35 U.S.C. § 102(b) as allegedly anticipated by Thogersen *et al* as evidenced by Kastrup *et al*, and as evidenced by the abstract of Nielsen *et al*. More specifically, the Examiner asserts that "Thogersen *et al* disclose the sequence for human tetranectin comprising the consensus sequence of Figure 2 and comprising residues E1 to K52, and a peptide construct pT7H6FX-TETN (page 91, lines 20-21) expressing the tetranectin monomer linked via a peptide bond at the N-terminus (page 91, lines 10 to 18 indicate fusion of the SEQ ID NO:37 to the tetranectin Glu1 residue) to heterologous sequence encoding a cleavage site for the bovine restriction protease." *See* Paper No. 16, Page 10, lines 14-18. Additionally, the Examiner states that

> it can be concluded that the oligomer construct of Thogersen *et al* is a trimer, said trimer comprising 3 heterologous moieties, as each tetranectin molecule in the trimer is fused to the heterologous protein. The trimeric oligomer construct exists as a triple alpha helical coiled-coil complex. This physical state is an inherent property of the tetranectin trimer.

Accordingly, the Examiner rejected claims 1, 19, 68-77, 83, 86, 90 and 98 under 35 U.S.C. § 102(b) as allegedly anticipated by Thogersen *et al* as evidenced by Kastrup *et al*, and as evidenced by the abstract of Nielsen *et al*.

In light of the amendments to Claim 1, Applicants respectfully disagree and traverse this rejection.

In order for a reference to anticipate under 35 U.S.C. § 102(b), the reference must disclose all limitations of the claimed invention in a printed publication in this or a foreign country more than one year prior to the date of application for patent in the United States. *See* MPEP § 2133. Thus in order for Thogersen *et al*, as evidenced by Kastrup *et al.* and Nielsen *et al.*, to be proper 35 U.S.C. § 102(b) art, all elements of the claimed invention must be described in a printed publication in this or a foreign country more than one year prior to the date of application for patent in the United States.

Thogersen *et al* fails this test.

As amended herein, pending claim 1 recites:

> 1. A monomer polypeptide construct comprising at least one tetranectin trimerising structural element (TTSE) which is covalently linked to at least one heterologous moiety, said TTSE being capable of forming a stable triple alpha helical coiled coil complex with two other TTSEs, where the heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FCTN23, the sequences of which are shown in SEQ ID NOs:24-27.

Thogersen *et al* disclose "the sequence for human tetranectin comprising the consensus sequence of Figure 2 and comprising residues E1 to K52, and a peptide construct pT7H6FX-TETN (page 91, lines 20-21) expressing the tetranectin monomer linked via a peptide bond at the N-terminus (page 91, lines 10 to 18 indicate fusion of the SEQ ID NO:37 to the tetranectin Glu1 residue) to heterologous sequence encoding a cleavage site for the bovine restriction protease." *See* Paper No. 16, Page 10, lines 14-18. The polypeptide produced by Example 9 of WO 94/18227 results in the sequence represented in the instant application as SEQ ID NO:25, which correlates to fusion protein H6FTXN123. As recited in amended claim 1, the claimed heterologous moiety covalently linked to the monomer polypeptide construct "is different from any of the fusion proteins ... H6FTXN123." The fusion protein in Thogersen *et al.* cited by the Examiner as the basis for the 35 U.S.C. § 102(b) rejection produces the fusion protein H6FTXN123. Fusion protein H6FXTN123 is specifically disclaimed from the subject matter of pending claim 1. As a result, International Publication No. WO 94/18227 is not available as proper § 102(b) prior art, as this reference does not meet all of the limitations of claim 1. Claims 19, 74, 75 and 76 ultimately incorporate all of the limitations of claim 1 through dependency. Therefore, International

Publication No. WO94/18227 is equally inapplicable as proper § 102(b) prior art against claims 19, 74, 75 and 76.

Similarly, claim 68 as amended herein includes the specific limitation that "said heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FCTN23, the sequences of which are shown in SEQ ID NOs:24-27." For the reasons set forth above, the fusion protein of Thogersen *et al.* cited by the Examiner as the basis for the 35 U.S.C. § 102(b) rejection, produces the fusion protein H6FTXN123 which is specifically excluded from the scope of amended claim 68.

As a result, Thogersen *et al* is equally inapplicable as proper § 102(b) prior art to claims 69-73, 77, 83, 86, 90 and 98, which depend from claim 68.

Accordingly, Thogersen *et al*, as evidenced by Kastrup *et al.* and Nielsen *et al.*, does not disclose all of the limitations of the claimed invention, and therefore is not available as proper 35 U.S.C. § 102(b) art against the instant invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 19, 68-77, 83, 86, 90 and 98 under 35 U.S.C. § 102(b) as allegedly anticipated by Thogersen *et al.* as evidenced by Kastrup *et al.* and Nielsen *et al.*

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 22, 23, 68-77, 82-90, 94, 98, 99, 102 and 103 under 35 U.S.C. § 103(a) as allegedly unpatentable over Thogersen *et al.* and Kastrup *et al.*, in view of Hoppe *et al.* More specifically, the Examiner asserts that "Thogersen *et al.*, as evidenced by Kastrup *et al.*, teach that tetranectin forms trimers in solution and in the crystal state." *See* Paper No. 16, Page 14, lines 4-5. Furthermore, the Examiner states that Hoppe *et al.* teach "trimerizing polypeptides comprising heterologous moieties attached N-terminally or C-terminally or both N and C terminally to a collectin-neck region polypeptide, said neck-region polypeptide able to form a trimer and the trimeric polypeptide complex comprising at least 2, 3, 4, 5 or 6 heterologous moieties." *See* Paper No. 16, Page 15, lines 2-5. The Examiner concludes that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the tetranectin monomer for the collectin neck region peptide disclosed by Hoppe *et al.* and symbolized by the structure on page 3, lines 11-16." *See* Paper 16, Page 16, lines 3-7. The Examiner further states that "substitution of the tetranectin monomer for the collectin neck region peptide would result in a monomer having the ability to trimerize as the collectin neck region peptide." *See* Paper 16, Page 16, lines 16-18.

Applicants respectfully disagree and traverse this rejection.

As stated by the Federal Circuit, "a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those or ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In addition, the prior art reference(s) must teach or suggest all of the claim limitations. The teaching or suggestion to combine and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *Id* at 493. *See also* M.P.E.P. § 2142. In order to find such motivation or suggestion, there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings. *See* M.P.E.P. § 2144.08(II)(A).

In the present case there is no motivation, suggestion or teaching to combine the references to arrive at the claimed invention. Neither the Thogersen *et al* reference, the Kastrup *et al* reference, or the Hoppe *et al* reference provides the requisite motivation, suggestion or teaching to those of ordinary skill in the art to combine the Thogersen *et al* reference, the Kastrup *et al* reference, and the Hoppe *et al* reference to arrive at Applicants' claimed invention.

In the present case, the Examiner has done no more than find the separate elements of the present invention and argue that broad disclosures which would require specific selection and experimentation to achieve the current invention, render the present invention obvious. The fact that each element of an invention may be found somewhere in the prior art is unavailing. A combination may be patentable whether it be composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments*, 221 USPQ 1, 7 (Fed. Cir. 1994).

In addition, it is of no doubt that one of ordinary skill in the art, enlightened by Applicants' teachings, would be motivated "with a reasonable expectation of success." *See* Paper 3, Page 16, lines 6-7. The issue remains, however, whether the necessary teaching, suggestion or motivation to combine the Thogersen *et al* reference, the Kastrup *et al* reference, and the Hoppe *et al* reference to arrive at Applicants' claimed invention was provided by the references themselves, and not Applicants' teachings. No proper teaching, suggestion or motivation to combine said references is provided by the Thogersen *et al* reference, the Kastrup *et al* reference, and the Hoppe *et al* reference, and accordingly,

Applicants' invention as claimed is not rendered obvious in light of the individual references or the combination thereof.

Nothwithstanding a lack of motivation to combine the Thogersen *et al* reference, the Kastrup *et al* reference, and the Hoppe *et al* reference, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. As stated in the M.P.E.P., "[e]vidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness. 'Evidence that a compound is unexpectedly superior in one of a spectrum of common properties...can be enough to rebut a prima facie case of obviousness.' No set number of examples of superiority is required." See M.P.E.P. § 716.02(a).

As explicitly recognized by the inventors of the instant application, "[t]he thermal stability of the tetranectin trimerisation module (as shown in the examples) is such that the trimer can be shown to exist even at about 60°C (Example 4, trimerised tetranectin) or at about 70°C (trimerized ubiquitin), whereas a collectin trimer unit falls apart at about 50-55°C (WO 95/31540, Example 1, page 36 therein)." *See* specification, page 6, first full paragraph. Accordingly, it is clearly seen that the thermal stability of the tetranectin trimerisation module of the present invention is significantly higher than the thermal stability of the prior art collectin-neck region trimeric polypeptide described by Hoppe *et al.* in WO 95/31540, which falls apart at about 50-55°C.

This surprising high thermal stability, as compared to the prior art collectin trimer, is further seen from the specification where it is stated that "a substantial part of the recombinant proteins exists in the oligomeric state of - and can be cross-linked as - trimeric molecules even at 70°C", (*See* specification, Page 15, lines 32-34); "SDS-PAGE analysis of reduced samples (Fig. 12) showed, that trimers are readily detectable even at 60°C", (*See* specification, Page 49, lines 35-37); and "...a substantial amount of trimer molecules is present even at 70°C" (*See* specification, Page 51, lines 33-34).

This improvement is surprising and unexpected in light of the prior art, and is significant. Assuming, *arguendo*, that it would be *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the tetranectin monomer for the collectin neck region peptide disclosed by Hoppe *et al.*, which it would not have been, one of ordinary skill in the art would expect to synthesize a trimeric polypeptide complex with a thermal stability having an upper limit of approximately 50-55°C. Contrary to the expectations of one of ordinary skill in the art, the inventors of the subject matter of the

instant application have generated trimeric polypeptides which are thermally stable, even at temperatures as high as 70°C in certain embodiments. This thermal stability is an extremely useful and unexpected trait that enables the provision of trimeric polypeptide carrier molecules having a high thermal stability, which do not disintegrate into monomer subunits even at relatively high temperatures. Consequently, by having this high thermal stability, the trimeric polypeptide molecules according to the invention would have no, or very few occurrences of exchange of monomer subunits between different trimeric polypeptide molecules, and hence the high thermal stability implies improved shelf life of the trimeric polypeptide molecules.

There are no teachings in association with trimerising structural elements derived from collectin which teach or suggest high thermal stability and improved shelf life on the order discovered by the inventors of the instant application.

These unexpected properties, disclosed by the Applicants in the priority filing, are substantial evidence that the invention as claimed was not *prima facie* obvious to one of ordinary skill in the art at the time of filing. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 22, 23, 68-77, 82-90, 94, 98, 99, 102 and 103 under 35 U.S.C. § 103(a) as allegedly unpatentable over Thogersen *et al.* and Kastrup *et al.*, in view of Hoppe *et al.*

The Examiner rejected claims 22, 23, 68-77, 82-91, 94, 102 and 103 under 35 U.S.C. § 103(a) as allegedly unpatentable over Thogersen *et al.*, Kastrup *et al.* and the abstract of Nielsen *et al* in view of Hoppe *et al.* and Baker *et al.* More specifically, the Examiner asserts that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the diagnostic agent comprising the trimeric polypeptide complex of tetranectin linked to an antibody and a detectable label as taught by the combination of Thogersen *et al*, Kastrup *et al*, and Nielsen *et al* and Hoppe *et al* for the anti-cardiotrophin-1 antibody, detectable label and kit comprising said antibody as taught by Baker *et al.*"

Applicants respectfully disagree and traverse this rejection.

As stated by the Federal Circuit, "a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those or ordinary skill would have a reasonable expectation of

success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In addition, the prior art reference(s) must teach or suggest all of the claim limitations. The teaching or suggestion to combine and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *Id* at 493. *See also* M.P.E.P. § 2142. In order to find such motivation or suggestion, there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings. *See* M.P.E.P. § 2144.08(II)(A).

In the present case there is no motivation, suggestion or teaching to combine the references to arrive at the claimed invention. Neither the Thogersen *et al* reference, the Kastrup *et al* reference, the Hoppe *et al* reference or the Baker *et al* reference provides the requisite motivation, suggestion or teaching to those of ordinary skill in the art to combine the Thogersen *et al* reference, the Kastrup *et al* reference, the Hoppe *et al* reference and the Baker *et al* reference to arrive at Applicants' claimed invention.

In the present case, the Examiner has done no more than find the separate elements of the present invention and argue that broad disclosures which would require specific selection and experimentation to achieve the current invention, render the present invention obvious. The fact that each element of an invention may be found somewhere in the prior art is unavailing. A combination may be patentable whether it be composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments*, 221 USPQ 1, 7 (Fed. Cir. 1994).

In view of the unexpected results discussed above, Applicants claimed invention was not obvious to one of ordinary skill in this art. More specifically, "[t]he thermal stability of the tetranectin trimerisation module (as shown in the examples) is such that the trimer can be shown to exist even at about 60°C (Example 4, trimerised tetranectin) or at about 70°C (trimerized ubiquitin), whereas a collectin trimer unit falls apart at about 50-55°C (WO 95/31540, Example 1, page 36 therein)." *See* specification, page 6, first full paragraph.

As discussed above, this improvement is surprising and unexpected in light of the prior art, and is significant. With a high thermal stability, trimeric polypeptides comprising the tetranectin trimerisation module has increased stability at elevated temperature (shown to exist even at 70°C) and increased shelf life. Accordingly, the trimeric polypeptides comprising the tetranectin trimerisation module are very useful as alternative trimeric polypeptide carrier molecules to be used in, e.g., protein library technology, diagnostic applications, and in a particularly preferred embodiment of the invention as therapeutic systems, such as pharmaceutical compositions.

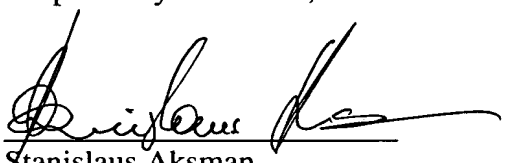
These unexpected properties, disclosed in the priority filing, are substantial evidence that the invention as claimed was not *prima facie* obvious to one of ordinary skill in the art at the time of filing. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 22, 23, 68-77, 82-91, 94, 102 and 103 under 35 U.S.C. § 103(a) as allegedly unpatentable over Thogersen *et al.*, Kastrup *et al.* and the abstract of Nielsen *et al* in view of Hoppe *et al.* and Baker *et al.*

Conclusion

Applicants believe that incorporation of the amendments and consideration of the above remarks have placed this application in a condition for allowance. Early notification of a favorable consideration is respectfully requested.

To the extent necessary, the Commissioner is authorized to grant any extension of time deemed needed for entry of this document and to charge additional fees associated with this communication or such extension of time or credit any overpayment to Deposit Account No. 50-0206.

Respectfully submitted,

Dated: December 2, 2002 By: 

Stanislaus Aksman
Registration No. 28,562
Robert C. Lampe, III
Registration No. 51,914

HUNTON & WILLIAMS
1900 K Street, N.W.
Suite 1200
Washington, D.C. 20006-1109
Telephone: (202) 955-1928
Facsimile: (202) 778-2201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number: 09/445,576

Examiner: Canella, K.

Filing Date: July 17, 2000

Art Unit: 1642

Title: Trimerising Module

Inventor: Thogersen, H., et al

Commissioner of Patents and Trademarks
Washington, D.C., 20231

APPENDIX A - Version with Markings to show Changes Made to the Specification

At Page 9, lines 3-11:

--Figure 3 depicts the construction of the expression plasmids pTH6FXtripa and pTH6FXtripb. Following the teachings of Example 1, tetranectin fusion proteins H6FXtripa (SEQ ID NO:28) and H6FXtripb (SEQ ID NO:29) are produced. To generate expression plasmids pTH6FXtripa and pTH6FXtripb, the polynucleotides encoding tetranectin fragments are ~~The amplified DNA fragments tripa (SEQ ID NO:40, bases 3-41 of which encode for residues 11-23 of SEQ ID NO:28, and SEQ ID NO:41 which encodes for residues 67-73 of SEQ ID NO:28) and tripb (SEQ ID NO:40, bases 3-41 of which encode for residues 11-23 of SEQ ID NO:28, while bases 1 and 2 are part of the codon for residue 10 of SEQ ID NO:28; and SEQ ID NO:42, which encodes for residues 64-69 of SEQ ID NO:29) harboring the tetranectin amino acid sequence (SEQ ID NO:7) from E1 to T48 and E1 to K52, respectively,~~ fused in the 5' end to nucleotide sequences encoding FX_a cleavage site IQGR (~~residues 3-6 of~~ SEQ ID NO:4103) and the recognition sites for the restriction endonucleases BglII and KpnI, were cut with the restriction enzymes BclI and HindIII and ligated into the BamHI ~~(SEQ ID NO:43 which encodes for residues 1-9 of SEQ ID NO:28)~~ and HindIII ~~(SEQ ID NO:44)~~ sites of the expression plasmid pT7H6 (Christensen et al., 1991) using standard techniques. ~~SEQ ID NOs: 40 and 41 are portions of a larger tripa DNA sequence; the dashes denote the unquoted portion of the DNA sequence. Likewise, SEQ ID NOs:40 and 42 are portions of the tripb DNA sequence, and SEQ ID NOs:43 and 44, of an unnamed DNA sequence.~~--

At Page 9, lines 18-30:

--Figure 5 depicts the generation of expression plasmids pTH6FXTN123 and pTCIIH6FXTN123. The amplified DNA fragment ~~corresponding to the full length,~~ encoding the mature tetranectin ~~monomer (SEQ ID NO:7) from E1 to V181~~ protein fragment is fused in the 5' end to nucleotide sequences encoding a FX_a cleavage site IEGR (~~residues 3-6 of~~ SEQ ID NO:~~10~~104). As is apparent from the teachings of Example 2, the N- and C-terminal residues of the mature tetranectin protein fragment are represented in Figure 5 as contained within amino acid fragments SEQ ID NO: 77 and SEQ ID NO: 78, respectively. This DNA was further cut with the restriction enzymes BamHI and HindIII and ligated into the corresponding sites of the expression plasmids pT7H6 (Christensen et al., 1991) and pT7CIIH6 using standard procedures. pT7CIIH6 was derived from pT7H6 by substitution of the NdeI-HindIII fragment of pT7H6 with the NdeI-HindIII fragment of pLcII (as disclosed by Nagai and Thogersen, 1987). ~~encoding the first 32 residues of the lambda cII protein MVRANKRNEALRIESALLNKIAMLGTEKTAEG (SEQ ID NO:11) fused in the 3' end to a nucleotide sequence encoding the H6 sequence GSHHHHHHGS (SEQ ID NO:12). In Fig. 5 the first sequence is a modified SEQ ID NO:7. The "EP" (Gly Pro) corresponds to amino acids 1-2 of SEQ ID NO:7, and the "IV" (Ile Val) to amino acids 180-181 of SEQ ID NO:7. The "--" corresponds to unquoted (but still present) DNA encoding amino acids 3-179 of SEQ ID NO:7. The sequence "GSIEGRGEP" (Gly Ser Ile Glu Gly Arg Gly Glu Pro) corresponds to amino acids 41-49 of SEQ ID NO:24, and the recited coding sequence for this nonpeptide is SEQ ID NO:45. The "--" denotes the unquoted DNA sequence joining SEQ ID NO:45 to the "ATCGTGTA" sequence.~~

~~In the next set of sequences, the "MVRA" (Met Val Arg Ala) corresponds to amino acids 1-4 of SEQ ID NO:24, and is encoded by SEQ ID NO:46. The "EGGSHHHHHH" (Glu Gly Gly Ser His His His His His His) corresponds to amino acids 31-40 of SEQ ID NO:24 and is encoded by SEQ IDNO:47. The "AGCTTGAATTC" is SEQ ID NO:48. The dashes denote unquoted DNA joining SEQ ID NO:46 to SEQ ID NO:47, and SEQ ID NO:47 to SEQ ID NO:48.~~

~~In the third set of sequences, the identifications are the same as for the first set.~~

~~In the fourth set of sequences, the "MGSHHHHHH" (Met Gly Ser His His His His His His) corresponds to amino acids 1-9 of SEQ ID NOs: 28 and 29, and is encoded by SEQ ID NO:43.~~--

At Page 10, lines 3-16:

--Figure 7 depicts the generation of expression plasmids pTH6FXTN12, pTH6FXTN23 and pTH6FXTN3. Amplified DNA fragments encoding tetranectin protein fragments are fused at their 5' end to nucleotide sequences encoding a FX_a cleavage site IEGR (SEQ ID NO: 104). These DNA fragments were further cut with the restriction enzymes BamHI and HindIII, and ligated into the corresponding sites of the expression plasmid pT7H6 (Christensen et al., 1991) using standard procedures. The resulting fusion proteins are represented by SEQ ID NOs: 26, 27 and 30, respectively. As is apparent from the teachings of Example 2, the N- and C-terminal residues of the tetranectin protein fragments contained with fusion proteins 26, 27 and 30 are represented in Figure 7 as contained within amino acid fragments SEQ ID NO: 82 and SEQ ID NO: 83, amino acid fragments SEQ ID NO: 84 and SEQ ID NO: 85, and amino acid fragments SEQ ID NO:86 and SEQ ID NO: 85, respectively. ~~The amplified DNA fragments corresponding to the tetranectin derivatives TN12 (SEQ ID NO:49 which encodes for residues 10-19 of SEQ ID NO:26 and SEQ ID NO:50) and TN3 from E1 to V49 and A45 to V181, respectively (SEQ ID NO:7) fused in the 5' end to nucleotide sequences encoding the FXa cleavage site IEGR (residues 3-6 of SEQ ID NO:10) was cut with the restriction enzymes BamHI and HindIII and ligated into the corresponding sites of the expression plasmids pT7H6 (Christensen et al., 1991) using standard procedures. The amplified DNA fragment corresponding to the tetranectin derivate TN23 from V17 to V181 (SEQ ID NO:7) fused in the 5' end to nucleotide sequences encoding the FXa cleavage site IQGR (residues 3-6 of SEQ ID NO:4) was cut with the restriction enzymes BamHI and HindIII and ligated into the corresponding sites of the expression plasmids pT7H6 (Christensen et al., 1991) using standard procedures.~~

~~In Fig. 7, in the line labeled "TN12", SEQ ID NO:49 encodes amino acids 10-19 of SEQ ID NO:26. Amino acids 17-19 of SEQ ID NO:26 correspond to amino acids 1-3 of SEQ ID NO:7. The "QTV" (Gln Thr Val) correspond to amino acids 47-49 of SEQ ID NO:7 and are encoded by SEQ ID NO:50.~~

~~In the line labeled "TN23", SEQ ID NO:51 encodes amino acids 10-19 of SEQ ID NO:27, and amino acids 16-19 of SEQ ID NO:27 correspond to amino acids 17-20 of SEQ ID NO:7. The "GIV" (Gly Ile Val) correspond to amino acids 179-181 of SEQ ID NO:7 and are encoded by SEQ ID NO:52.~~

~~In the line labeled "TN3", SEQ ID NO:53 encodes amino acids 10-19 of SEQ ID NO:30. Amino acids 17-19 of SEQ ID NO:30 correspond to amino acids 45-47 of SEQ ID NO:7 and are encoded by SEQ ID NO:54.~~

~~In the unlabeled line, SEQ ID NO:43 encodes amino acids 1-9 of SEQ ID NO:30, and the AGCTTGAATTC is SEQ ID NO:44.--~~

At Page 12, between lines 8 and 9:

~~--In Fig. 13, the sequence "GSQIFV" (Gly Ser Gln Ile Phe Val) corresponds to amino acids 68-73 of SEQ ID NO:31, and is encoded by SEQ ID NO:55. The "RGGS" (Arg Gly Gly Ser) corresponds to amino acids 142-145 of SEQ ID NO:31, and is encoded by SEQ ID NO:56. For other sequences, see the description of Figure 3, but note that the "GAATTC" are bases 6-11 of SEQ ID NO:44.--~~

At Page 12, between lines 20 and 21:

~~--In Fig. 15, "SQVQL" (Ser Gln Val Gln Leu) correspond to amino acids 16-20 of SEQ ID NO:32, and are encoded by SEQ ID NO:57. "LNGA" (Leu Asn Gly Ala) correspond to amino acids 275-278 of SEQ ID NO:32, and are encoded by SEQ ID NO:58. In the second set, the first amino acid sequence corresponds to amino acids 1-23 of SEQ ID NO:33 and is encoded by SEQ ID NO:59, and the second to amino acids 64-69 of SEQ ID NO:## and is encoded by SEQ ID NO:60 (which also includes SEQ ID NO:42, comapre Figure 3).--~~

At Page 12, lines 26-32:

--The DNA fragment, amplified with the primer pairs having SEQ ID NO:21 and 23, comprising the nucleotide sequence (SEQ ID NO:20) encoding the single chain antibody CEA6, scFV (CEA6), amino acid sequence from Q1 to A261 was cut with the restriction enzymes BamHI and HindIII and ligated into the BamHI and HindIII sites of the expression plasmid pT7H6FXtripb (Example 1) using standard procedures. ~~The sequences of Fig. 17 were identified above in connection with Fig. 15.~~--

At Page 13, between lines 12 and 13:

~~--The sequences of Fig. 19 were identified above in connection with Fig. 15. Generally, in Figures 13, 15, 17, and 19, dashes denote unquoted DNA sequences.--~~

At Page 15, line 30 extending to page 16, line 16:

--The TTSEs form surprisingly stable trimeric molecules (Examples 2, 3, and 4). The experimental observations, that **(1)** a substantial part of the recombinant proteins exists in the oligomeric state of$_1$ - and can be cross-linked as$_1$ - trimeric molecules even at 70°C and **(2)** that exchange of monomers between different trimers can only be detected after exposure to elevated temperature are evidence of a extremely high stability of the tetranectin trimerising structural element. This feature must be reflected in the amino acid sequence of the structural element. In particular, the presence and position of the glutamine containing repeat in the sequential array of heptad repeats is, together with the presence and relative position of the other conserved residues in the consensus sequence (Fig. 2), considered important for the formation of these stable trimeric molecules. For most practical uses the cysteine residue 50 should be mutagenized to serine, threonine, methionine or to any other amino acid residue in order to avoid formation of an unwanted inter-chain disulphide bridge, which eventually would lead to uncontrolled multimerisation, aggregation and precipitation of a polypeptide product harbouring this sequence.--

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number: 09/445,576

Examiner: Canella, K.

Filing Date: July 17, 2000

Art Unit: 1642

Title: Trimerising Module

Inventor: Thogersen, H., et al

Commissioner of Patents and Trademarks
Washington, D.C., 20231

APPENDIX B - Version with Markings to show Changes Made to the Claims

1 (twice amended). A monomer polypeptide construct comprising at least one tetranectin trimerising structural element (TTSE) which is covalently linked to at least one heterologous ~~moeity~~moiety, said TTSE being capable of forming a stable triple alpha helical coiled coil complex with two other TTSEs, where ~~(a)~~ the heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12~~M~~, H6FCTN23, the sequences of which are shown in SEQ ID NOs:24-27~~; and/or (b) at least one heterologous moiety being one in which does not exclusively facilitate expression and/or purification of the monomer polypeptide construct~~.

22 (twice amended). A~~n~~ trimeric polypeptide complex according to claim 68, wherein the at least one heterologous moiety ~~which is~~ positioned N-terminally to a TTSE and the at least one heterologous moiety ~~which is~~ positioned C-terminally to a TTSE are part of the same monomer polypeptide.

23 (twice amended). A~~n~~ trimeric polypeptide complex according to claim 68, wherein the at least one heterologous moiety ~~which is~~ positioned N-terminally to a TTSE and the at least one heterologous moiety ~~which is~~ positioned C-terminally to a TTSE are part of two separate monomer polypeptides.

68 (amended). A trimeric polypeptide complex comprising three monomer polypeptides, wherein (i) each of said monomer polypeptides comprises a tetranectin trimerising structural element (TTSE), said TTSE being a polypeptide having at least 68% amino acid sequence identity with the consensus sequence shown in Fig. 2, and (ii) at least one of said monomer polypeptides is covalently linked to at least one heterologous moiety~~.~~, where said at least one heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FCTN23, the sequences of which are shown in SEQ ID NOs:24-27.

76 (amended). The trimeric polypeptide complex according to claim 75, wherein the TTSE derived from human tetranectin further comprises the amino acid residues C50 to K52 ~~(exon 3)~~ of exon 3 as shown in Figure 1.

82 (amended). The trimeric polypeptide complex according to claim 68 ~~which is stable~~ wherein the complex remains substantially as a trimer in the temperature range 50-70°C.

84 (amended). The trimeric polypeptide complex according to claim 68, wherein the at least one heterologous moiety is selected from the group consisting of ~~a ligand binding structure; a toxin; a detectable label; an in situ activatable substance; an enzyme; a radioactive moiety; a cytokine; a non-proteinaceous polymer such as a polymeric alkaloid, a polyalcohol, a polysaccharide, a lipid and a polyamine; a photo cross-linking agent; and a group facilitating conjugation of the polypeptide to a target.~~:

(a) a ligand binding structure;

(b) a toxin;

(c) a detectable moiety;

(d) an in situ activatable substance;

(e) an enzyme;

(f) a radioactive moiety;

(g) a cytokine;

(h) a non-proteinaceous polymer;

(i) a polyalcohol;

(j) a polysaccharide;

(k) a lipid;

(l) a polyamine;

(m) a photo cross-linking agent; and

(n) a group facilitating conjugation of the polypeptide to a target, wherein the conjugation encompasses both covalent and non-covalent linkages.

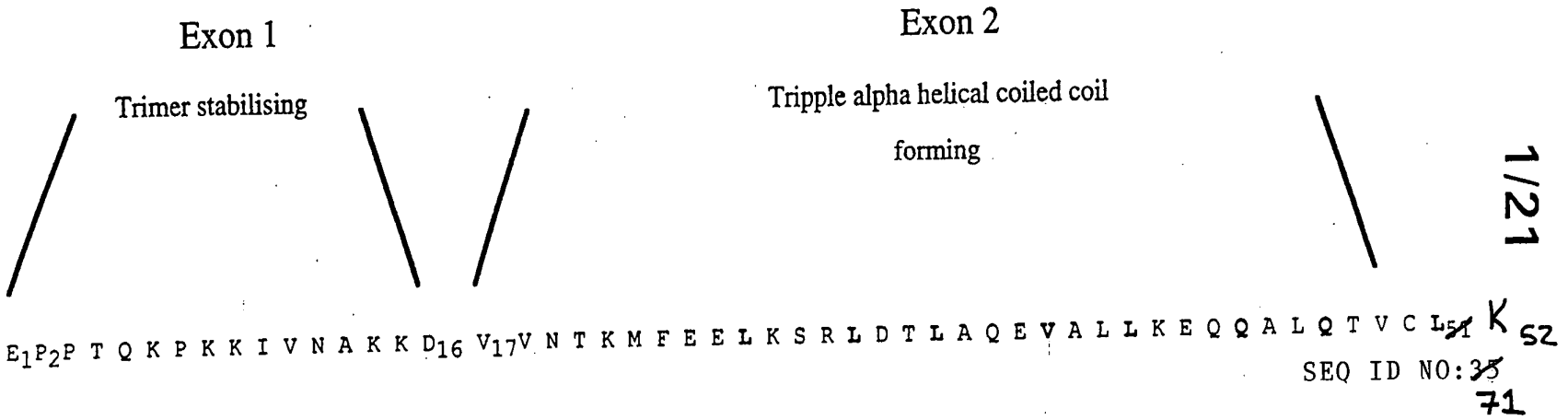
87 (amended). The trimeric polypeptide complex according to claim 68, which comprises at least one heterologous moiety which is positioned N-terminally to ~~the~~ at least one monomer polypeptide and at least one heterologous moiety which is positioned C-terminally to ~~the~~ at least one monomer polypeptide.

88 (amended). The trimeric polypeptide complex according to claim 68, wherein the at least one heterologous moiety is covalently linked to the monomer polypeptide via a peptide bond to the N- or C-terminus of the monomer polypeptide chain, via a peptide bond to a side chain in the monomer polypeptide, via a bond to a cysteine residue, or when more than one heterologous moiety, combinations of these locations.

90 (amended). A method for preparing a trimeric polypeptide complex which comprises (i) admixing three monomer polypeptides according to claim 68, (ii) effecting complex formation between said monomer polypeptides, and (iii) isolating the resulting trimeric polypeptide complex ~~and optionally subjecting the polypeptide complex to further processing~~.

94 (amended). A chimeric product comprising a trimeric polypeptide complex according to claim 68, wherein said product ~~having low antigenicity in humans relative to formulations comprising one or more components of non-human origin~~does not elicit an antigenic response in a human subject.

101 (amended). The method according to claim 100 wherein the composition is administered by a route selected from the group consisting of the intravenous route, the intraarterial route, the transmembraneus route of the buccal, anal ~~e~~or vaginal tissue, intranasal route, the pulmonary route, the transdermal route, intramuscular, subcutaneous, intratechal, ~~the buccal,~~ inoculation into tissue, or by an implant.



SEQ ID NO: 35 71

Fig. 1

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Murine tetranectin	L V S S K M F E E L K N R M D V L A Q E V A L L K E K Q A L Q T V C L K	SEQ ID NO:37
Bovine cart. protein	R R V K E K D G D L K T Q V E K L W R E V N A L K E M Q A L Q T V C L R	SEQ ID NO:38
Shark cart. protein	S K S G K G K D D L R N E I D K L W R E V N S L K E M Q A L Q T V C L K	SEQ ID NO:39
Consensus	X X X X X X X X L X X X X L X X E V X X L K E X Q A L Q T V C L X	SEQ ID NO:40

Fig. 2

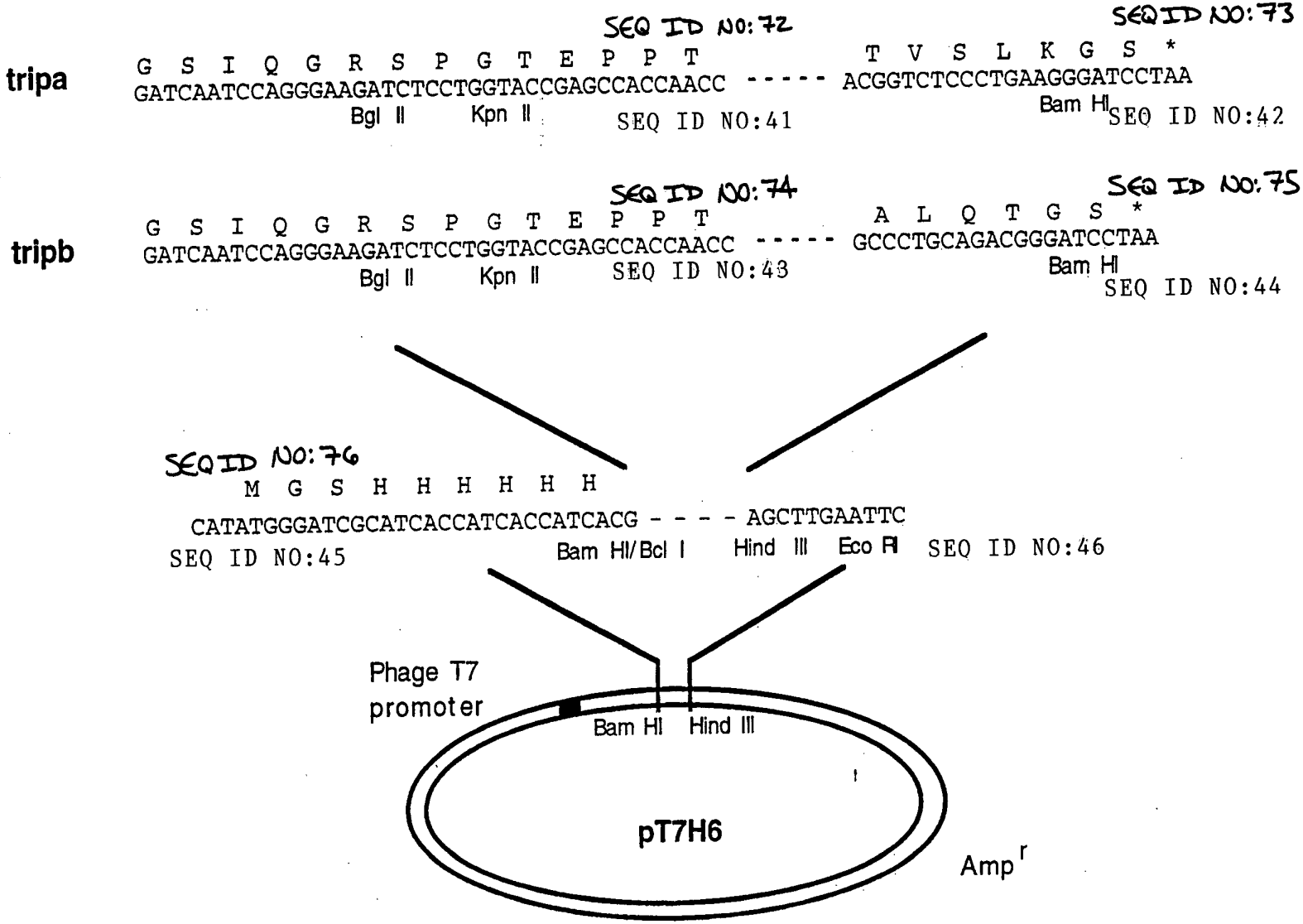
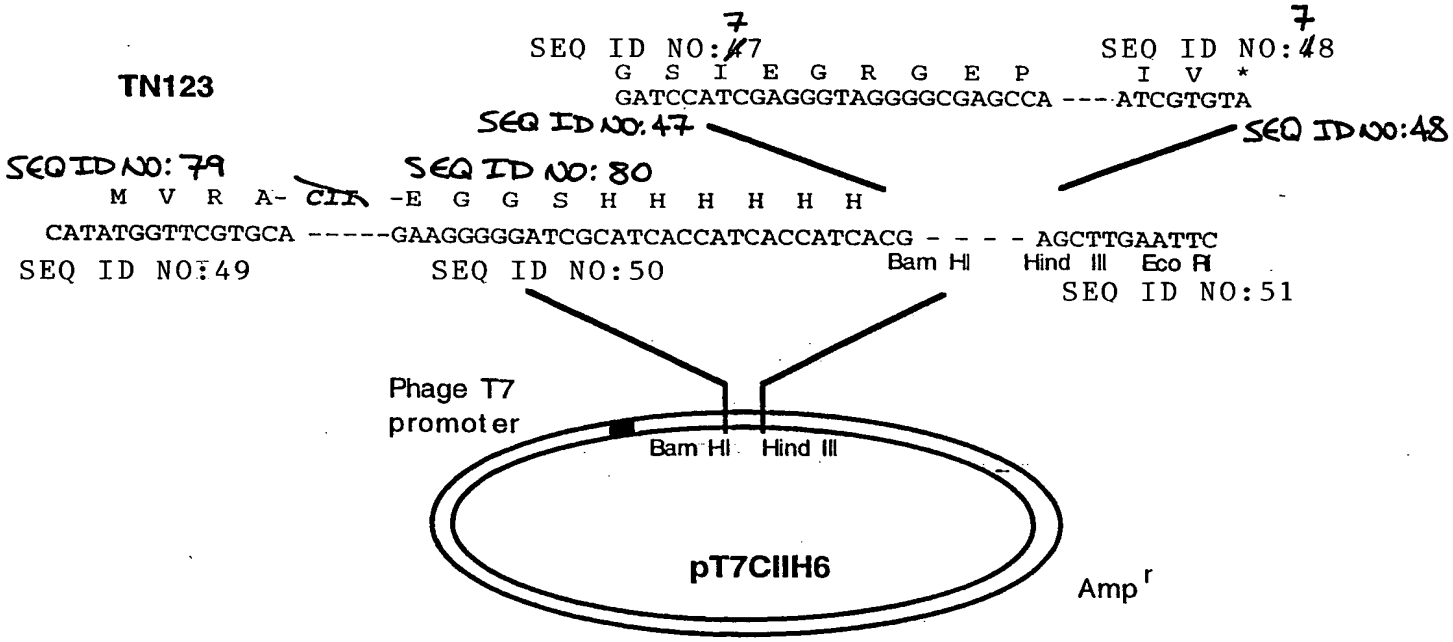


Fig. 3



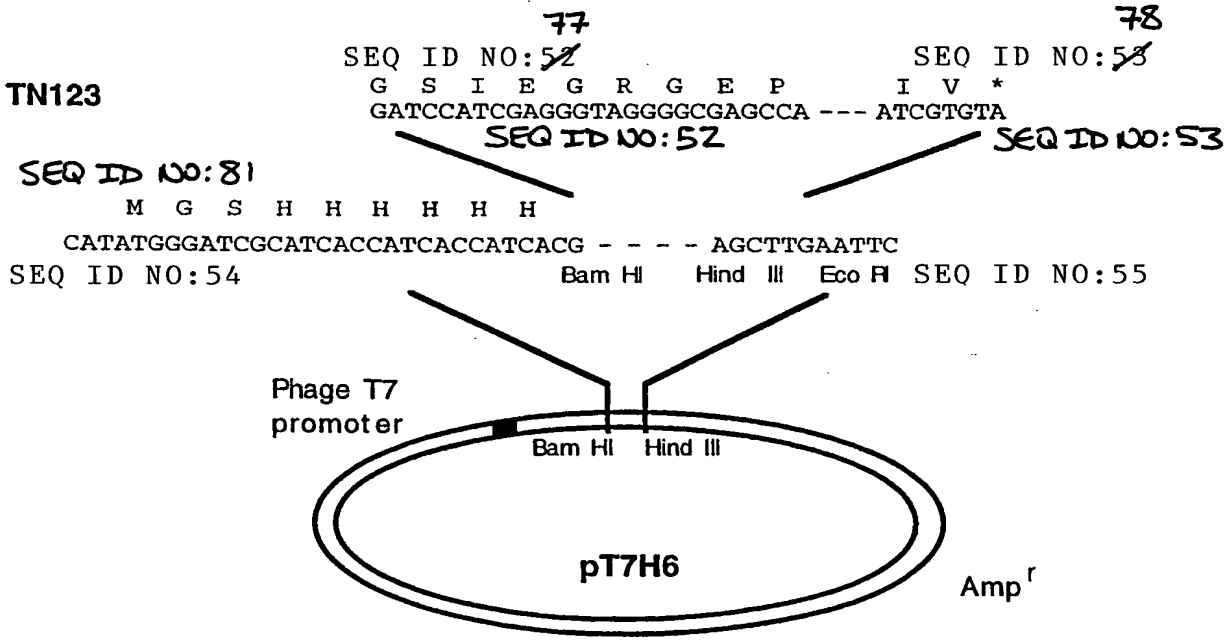


Fig. 5

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151 V G N E A E I W L G L N D M A A E G T W V D M T G A R I A Y 180
181 K N W E T E I T A Q P D G G K T E N C A V L S G A A N G K W 210
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H6FXTN123 fusion protein SEO ID NO: ~~24~~ 25

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Fig. 6

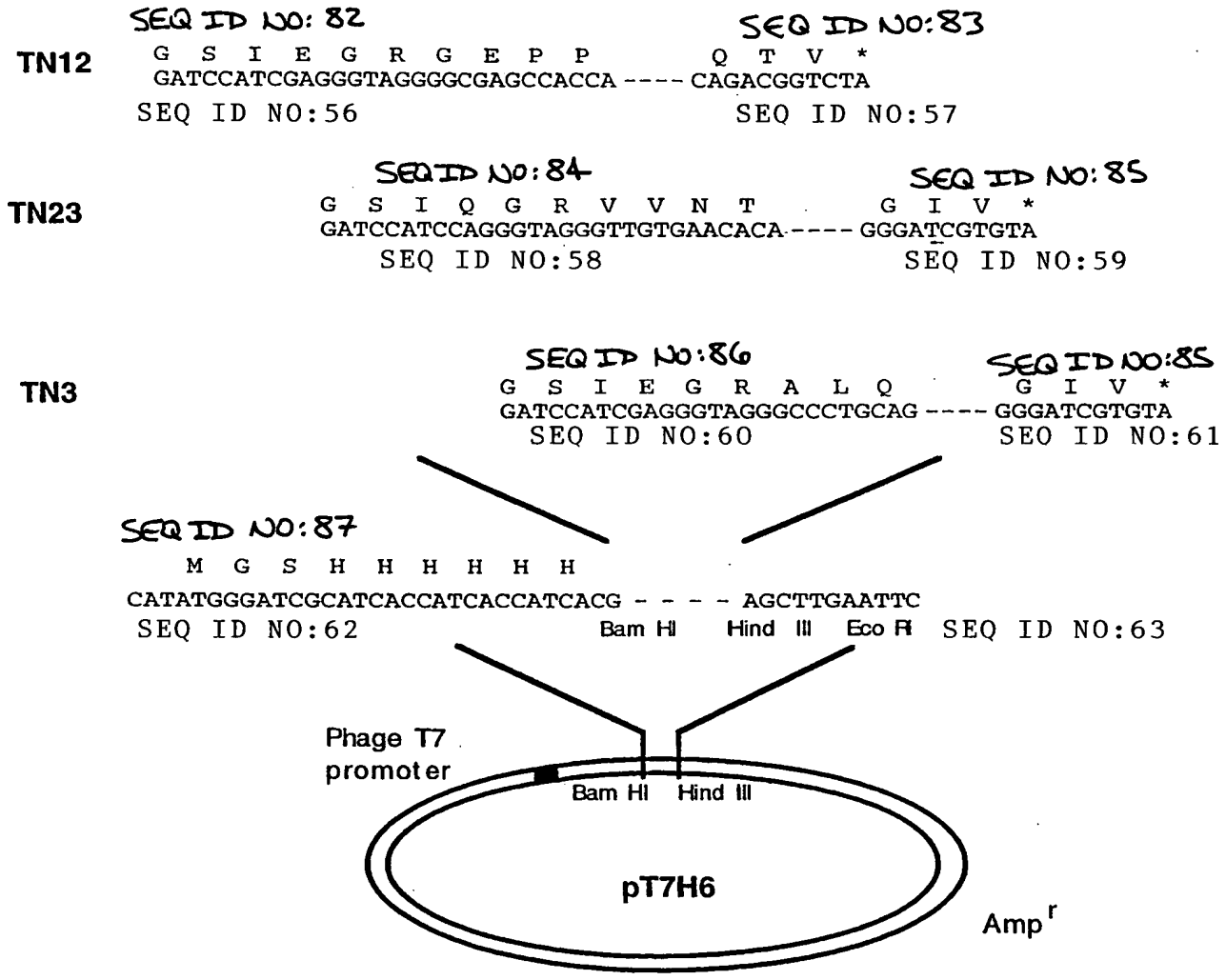

Fig. 7

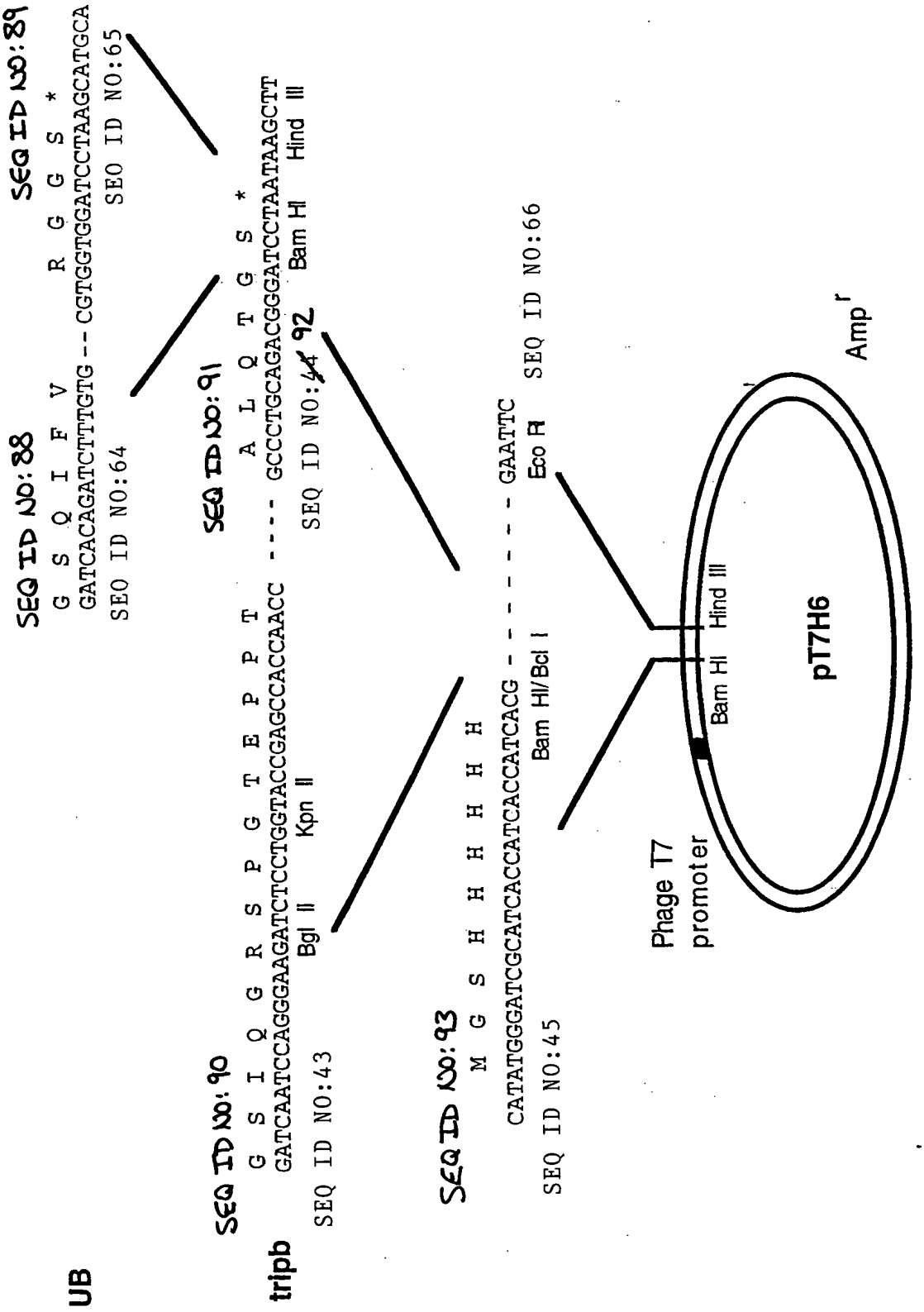

Fig. 13

Fig. 13

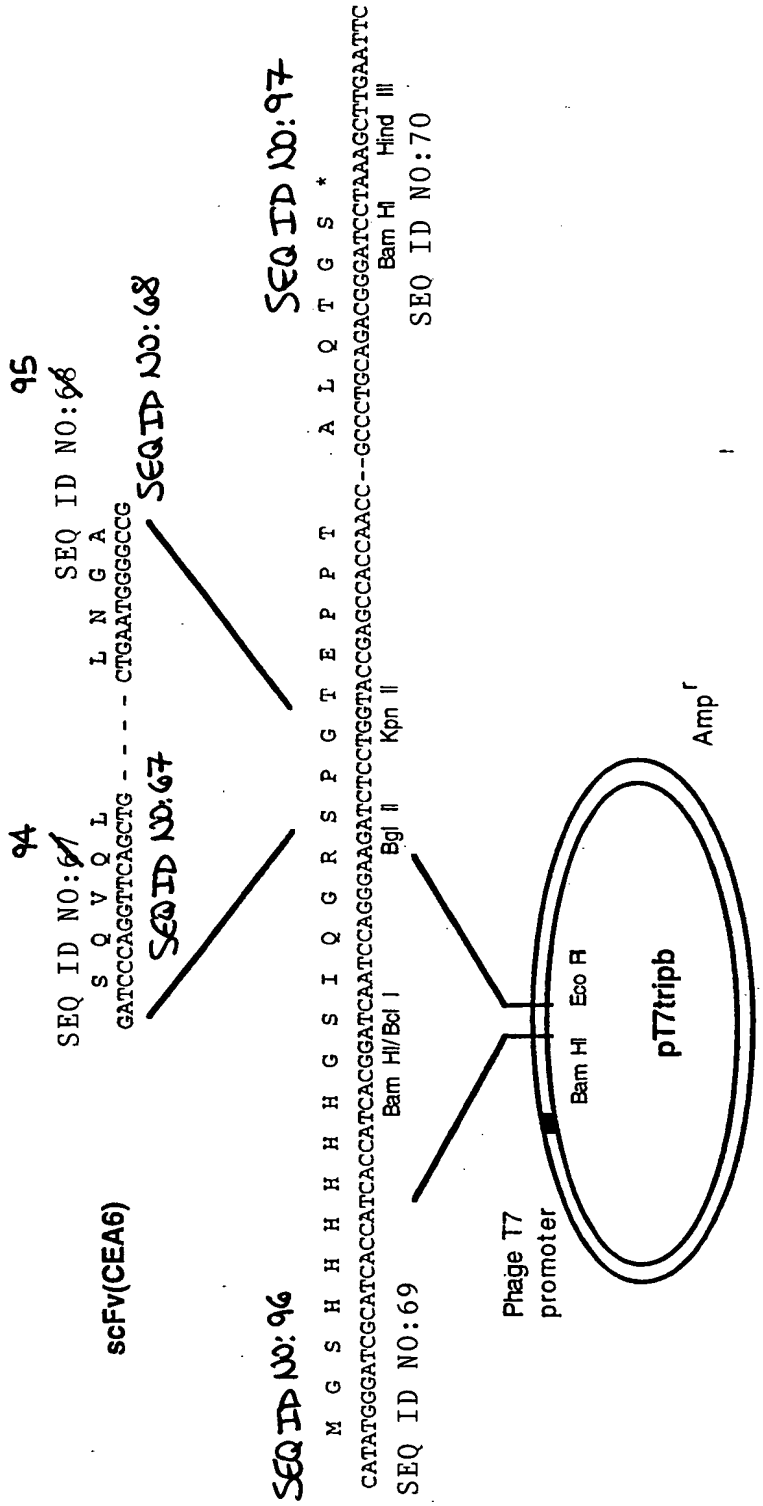

Fig. 15

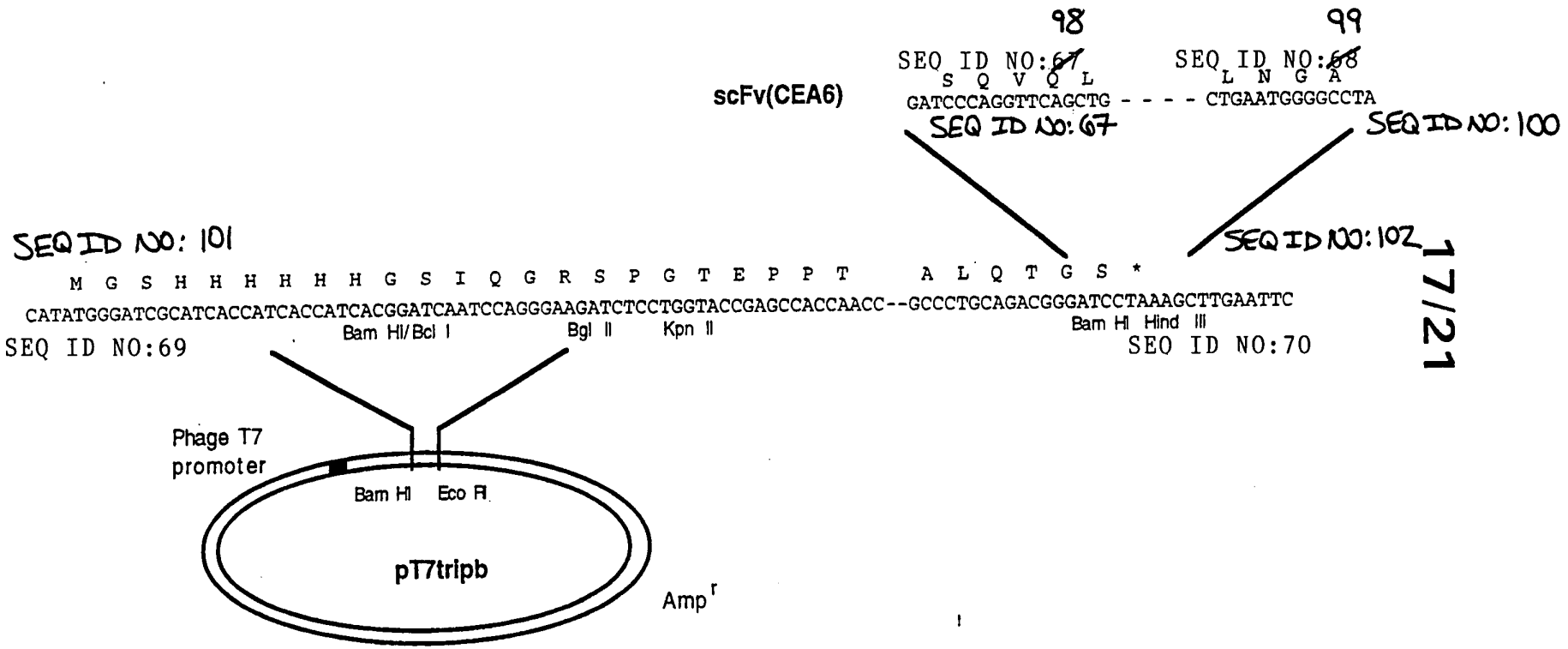

Fig. 17

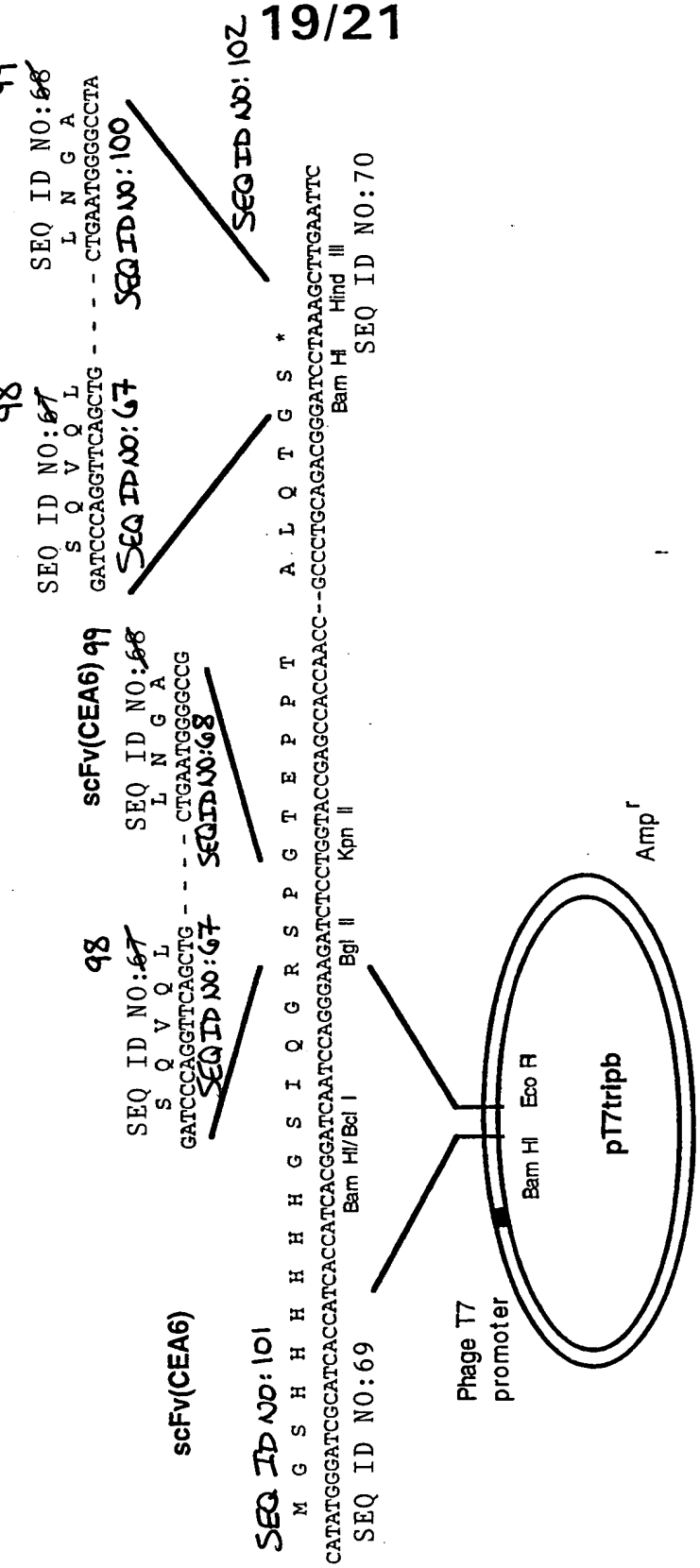

Fig. 19

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35 40 45

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65 70 75 80

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65                  70                  75                  80

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Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu Ala Glu Ile Trp Leu Gly
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        35                  40                  45

Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala Leu Gln Thr
    50                  55                  60

Val Cys Leu Lys Gly Thr Lys Val His Met Lys Cys Phe Leu Ala Phe
65                  70                  75                  80

Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu Asp Cys Ile Ser Arg
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Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu Ile Thr Ala Gln Pro
145                 150                 155                 160

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Cys Leu Lys Gly Thr Lys Val His Met Lys Cys Phe Leu Ala Phe Thr
50 55 60

Gln Thr Lys Thr Phe His Glu Ala Ser Glu Asp Cys Ile Ser Arg Gly
65 70 75 80

```
Gly Thr Leu Ser Thr Pro Gln Thr Gly Ser Glu Asn Asp Ala Leu Tyr
                85                  90                  95

Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu Ala Glu Ile Trp Leu Gly
            100                 105                 110

Leu Asn Asp Met Ala Ala Glu Gly Thr Trp Val Asp Met Thr Gly Ala
        115                 120                 125

Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu Ile Thr Ala Gln Pro Asp
    130                 135                 140

Gly Gly Lys Thr Glu Asn Cys Ala Val Leu Ser Gly Ala Ala Asn Gly
145                 150                 155                 160

Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln Leu Pro Tyr Ile Cys Gln
                165                 170                 175

Phe Gly Ile Val
            180
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<210> 28
<211> 73
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<220>
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<400> 28

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Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1               5                   10                  15

Pro Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala
            20                  25                  30

Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg
        35                  40                  45

Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala
    50                  55                  60

Leu Gln Thr Val Ser Leu Lys Gly Ser
65                  70
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<210> 29
<211> 69
<212> PRT

<213> Artificial

<220>
<223> H6FXtripb

<400> 29

Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1 5 10 15

Pro Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala
20 25 30

Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg
35 40 45

Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala
50 55 60

Leu Gln Thr Gly Ser
65

<210> 30
<211> 152
<212> PRT
<213> Artificial

<220>
<223> H6FXTN3

<400> 30

Met Gly Ser His His His His His His Gly Ser Ile Glu Gly Arg Ala
1 5 10 15

Leu Gln Thr Val Cys Leu Lys Gly Thr Lys Val His Met Lys Cys Phe
20 25 30

Leu Ala Phe Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu Asp Cys
35 40 45

Ile Ser Arg Gly Gly Thr Leu Ser Thr Pro Gln Thr Gly Ser Glu Asn
50 55 60

Asp Ala Leu Tyr Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu Ala Glu
65 70 75 80

Ile Trp Leu Gly Leu Asn Asp Met Ala Ala Glu Gly Thr Trp Val Asp
85 90 95

Met Thr Gly Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu Ile Thr
100 105 110

Ala Gln Pro Asp Gly Gly Lys Thr Glu Asn Cys Ala Val Leu Ser Gly
115 120 125

Ala Ala Asn Gly Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln Leu Pro
130 135 140

Tyr Ile Cys Gln Phe Gly Ile Val
145 150

<210> 31
<211> 145
<212> PRT
<213> Artificial

<220>
<223> H6FXtripb-UB

<400> 31

Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1 5 10 15

Pro Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala
20 25 30

Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg
35 40 45

Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala
50 55 60

Leu Gln Thr Gly Ser Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr
65 70 75 80

Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala
85 90 95

Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile
100 105 110

Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn
115 120 125

Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly
130 135 140

Ser
145

<210> 32
<211> 330
<212> PRT
<213> Artificial

<220>
<223> H6FXscFv(CEA6)-TRIPB

<400> 32

Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1 5 10 15

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
20 25 30

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Ser
35 40 45

Pro Ile Asn Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
50 55 60

Gly Ser Ile Ile Pro Ser Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
65 70 75 80

Gln Gly Arg Leu Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
85 90 95

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
100 105 110

Ala Gly Arg Ser His Asn Tyr Glu Leu Tyr Tyr Tyr Tyr Met Asp Val
115 120 125

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln
145 150 155 160

Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr
165 170 175

Cys Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln
180 185 190

```
Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu
        195                 200                 205

Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr
                245                 250                 255

Lys Leu Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser Glu
            260                 265                 270

Glu Asp Leu Asn Gly Ala Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys
        275                 280                 285

Lys Ile Val Asn Ala Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu
    290                 295                 300

Glu Leu Lys Ser Arg Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu
305                 310                 315                 320

Lys Glu Gln Gln Ala Leu Gln Thr Gly Ser
                325                 330
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<210> 33
<211> 331
<212> PRT
<213> Artificial

<220>
<223> H6FXTRIPB-scFv(CEA6)

<400> 33

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Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1               5                   10                  15

Pro Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala
            20                  25                  30

Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg
        35                  40                  45

Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala
```

```
    50                  55                  60

Leu Gln Thr Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val
65                  70                  75                  80

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly
                85                  90                  95

Thr Phe Ser Asn Ser Pro Ile Asn Trp Leu Arg Gln Ala Pro Gly Gln
            100                 105                 110

Gly Leu Glu Trp Met Gly Ser Ile Ile Pro Ser Phe Gly Thr Ala Asn
        115                 120                 125

Tyr Ala Gln Lys Phe Gln Gly Arg Leu Thr Ile Thr Ala Asp Glu Ser
    130                 135                 140

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
145                 150                 155                 160

Ala Val Tyr Tyr Cys Ala Gly Arg Ser His Asn Tyr Glu Leu Tyr Tyr
                165                 170                 175

Tyr Tyr Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
            180                 185                 190

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
        195                 200                 205

Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly Asp
    210                 215                 220

Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp Leu
225                 230                 235                 240

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                245                 250                 255

Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly Ser
            260                 265                 270

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
        275                 280                 285

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu Thr
    290                 295                 300
```

```
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Glu Gln
305                 310                 315                 320

Lys Leu Ile Ser Glu Glu Asp Leu Asn Gly Ala
                325                 330
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<210> 34
<211> 592
<212> PRT
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<220>
<223> H6FXscFv(CEA6)tripbscFv(CEA6)

<400> 34

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Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1               5                   10                  15

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
            20                  25                  30

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Ser
        35                  40                  45

Pro Ile Asn Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
    50                  55                  60

Gly Ser Ile Ile Pro Ser Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
65                  70                  75                  80

Gln Gly Arg Leu Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
                85                  90                  95

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
            100                 105                 110

Ala Gly Arg Ser His Asn Tyr Glu Leu Tyr Tyr Tyr Tyr Met Asp Val
        115                 120                 125

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln
145                 150                 155                 160

Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr
```

```
                 165                 170                 175

Cys Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln
             180                 185                 190

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu
         195                 200                 205

Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
     210                 215                 220

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr
                245                 250                 255

Lys Leu Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser Glu
             260                 265                 270

Glu Asp Leu Asn Gly Ala Gly Thr Glu Pro Pro Thr Gln Lys Pro Lys
         275                 280                 285

Lys Ile Val Asn Ala Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu
     290                 295                 300

Glu Leu Lys Ser Arg Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu
305                 310                 315                 320

Lys Glu Gln Gln Ala Leu Gln Thr Gly Ser Gln Val Gln Leu Gln Gln
                325                 330                 335

Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys
             340                 345                 350

Lys Ala Ser Gly Gly Thr Phe Ser Asn Ser Pro Ile Asn Trp Leu Arg
         355                 360                 365

Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Ser Ile Ile Pro Ser
     370                 375                 380

Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln Gly Arg Leu Thr Ile
385                 390                 395                 400

Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu
                405                 410                 415
```

```
Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Arg Ser His Asn
            420                 425                 430

Tyr Glu Leu Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Gln Gly Thr Met
        435                 440                 445

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    450                 455                 460

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser
465                 470                 475                 480

Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly
                485                 490                 495

Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
            500                 505                 510

Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser
        515                 520                 525

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
    530                 535                 540

Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser
545                 550                 555                 560

Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
                565                 570                 575

Ala Ala Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn Gly Ala
            580                 585                 590
```

<210> 35
<211> 51
<212> PRT
<213> Homo sapiens

<400> 35

```
Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala Lys Lys Asp
1               5                   10                  15

Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg Leu Asp Thr
            20                  25                  30
```

Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala Leu Gln Thr
35 40 45

Val Cys Leu
50

<210> 36
<211> 36
<212> PRT
<213> Homo sapiens

<400> 36

Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg Leu Asp Thr
1 5 10 15

Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala Leu Gln Thr
20 25 30

Val Cys Leu Lys
35

<210> 37
<211> 36
<212> PRT
<213> Murine

<400> 37

Leu Val Ser Ser Lys Met Phe Glu Glu Leu Lys Asn Arg Met Asp Val
1 5 10 15

Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Lys Gln Ala Leu Gln Thr
20 25 30

Val Cys Leu Lys
35

<210> 38
<211> 36
<212> PRT
<213> Bovine

<400> 38

Arg Arg Val Lys Glu Lys Asp Gly Asp Leu Lys Thr Gln Val Glu Lys
1 5 10 15

Leu Trp Arg Glu Val Asn Ala Leu Lys Glu Met Gln Ala Leu Gln Thr
20 25 30

Val Cys Leu Arg
35

<210> 39
<211> 36
<212> PRT
<213> Shark

<400> 39

Ser Lys Ser Gly Lys Gly Lys Asp Asp Leu Arg Asn Glu Ile Asp Lys
1 5 10 15

Leu Trp Arg Glu Val Asn Ser Leu Lys Glu Met Gln Ala Leu Gln Thr
20 25 30

Val Cys Leu Lys
35

<210> 40
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<400> 40

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Leu Xaa Xaa Glu Val Xaa Xaa Leu Lys Glu Xaa Gln Ala Leu Gln Thr
20 25 30

Val Cys Leu Xaa
35

<210> 41
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<212> DNA
<213> Artificial

<220>
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<400> 41
gatcaatcca gggaagatct cctggtaccg agccaccaac c 41

<210> 42
<211> 24
<212> DNA
<213> Artificial

<220>
<223> tripa

<400> 42
acggtctccc tgaagggatc ctaa 24

<210> 43
<211> 41
<212> DNA
<213> Artificial

<220>
<223> tripb

<400> 43
gatcaatcca gggaagatct cctggtaccg agccaccaac c 41

<210> 44
<211> 21
<212> DNA
<213> Artificial

<220>
<223> tripb

<400> 44
gccctgcaga cgggatccta a 21

<210> 45
<211> 31
<212> DNA
<213> Artificial

<220>
<223> pT7H6

<400> 45
catatgggat cgcatcacca tcaccatcac g 31

<210> 46
<211> 11
<212> DNA
<213> Artificial

<220>
<223> pT7H6

<400> 46
agcttgaatt c 11

<210> 47
<211> 26
<212> DNA
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<220>
<223> TN123

<400> 47
gatccatcga gggtaggggc gagcca 26

<210> 48
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<212> DNA
<213> Artificial

<220>
<223> tn123

<400> 48
atcgtgta 8

<210> 49
<211> 15
<212> DNA
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<220>

<223> pT7CIIH6

<400> 49
catatggttc gtgca 15

<210> 50
<211> 31
<212> DNA
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<220>
<223> pT7CIIH6

<400> 50
gaaggggat cgcatcacca tcaccatcac g 31

<210> 51
<211> 11
<212> DNA
<213> Artificial

<220>
<223> pT7CIIH6

<400> 51
agcttgaatt c 11

<210> 52
<211> 26
<212> DNA
<213> Artificial

<220>
<223> TN123

<400> 52
gatccatcga gggtaggggc gagcca 26

<210> 53
<211> 8
<212> DNA
<213> Artificial

<220>
<223> TN123

<400> 53
atcgtgta 8

<210> 54
<211> 31
<212> DNA
<213> Artificial

<220>
<223> pT7H6

<400> 54
catatgggat cgcatcacca tcaccatcac g 31

<210> 55
<211> 11
<212> DNA
<213> Artificial

<220>
<223> pT7H6

<400> 55
agcttgaatt c 11

<210> 56
<211> 29
<212> DNA
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<220>
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<400> 56
gatccatcga gggtaggggc gagccacca 29

<210> 57
<211> 11
<212> DNA
<213> Artificial

<220>
<223> TN12

<400> 57
cagacggtct a 11

<210> 58
<211> 29
<212> DNA
<213> Artificial

<220>
<223> TN23

<400> 58
gatccatcca gggtagggtt gtgaacaca 29

<210> 59
<211> 11
<212> DNA
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<220>
<223> TN23

<400> 59
gggatcgtgt a 11

<210> 60
<211> 26
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<220>
<223> TN3

<400> 60
gatccatcga gggtagggcc ctgcag 26

<210> 61
<211> 11
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<220>
<223> TN3

<400> 61
gggatcgtgt a 11

<210> 62
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<212> DNA
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<220>
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<400> 62
catatgggat cgcatcacca tcaccatcac g 31

<210> 63
<211> 11
<212> DNA
<213> Artificial

<220>
<223> pT7H6

<400> 63
agcttgaatt c 11

<210> 64
<211> 17
<212> DNA
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<220>
<223> UB

<400> 64

gatcacagat ctttgtg 17

<210> 65
<211> 22
<212> DNA
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<220>
<223> UB

<400> 65
cgtggtggat cctaagcatg ca 22

<210> 66
<211> 6
<212> DNA
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<220>
<223> pT7H6

<400> 66
gaattc 6

<210> 67
<211> 17
<212> DNA
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<220>
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<400> 67
gatcccaggt tcagctg 17

<210> 68
<211> 13
<212> DNA
<213> Artificial

<220>
<223> scFv(CEA6)

<400> 68
ctgaatgggg ccg 13

<210> 69
<211> 72
<212> DNA
<213> Artificial

<220>
<223> pT7tribb

<400> 69
catatgggat cgcatcacca tcaccatcac ggatcaatcc agggaagatc tcctggtacc 60

gagccaccaa cc 72

<210> 70
<211> 32
<212> DNA
<213> Artificial

<220>
<223> pT7tripb

<400> 70
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<210> 71
<211> 52
<212> PRT
<213> Homo sapiens

<400> 71

Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala Lys Lys Asp
1 5 10 15

Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys Ser Arg Leu Asp Thr
20 25 30

Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln Gln Ala Leu Gln Thr
35 40 45

Val Cys Leu Lys
50

<210> 72
<211> 14
<212> PRT
<213> Artificial

<220>
<223> tripa

<400> 72

Gly Ser Ile Gln Gly Arg Ser Pro Gly Thr Glu Pro Pro Thr
1 5 10

<210> 73
<211> 7
<212> PRT
<213> Artificial

<220>
<223> tripa

<400> 73

Thr Val Ser Leu Lys Gly Ser
1 5

<210> 74
<211> 14
<212> PRT
<213> Artificial

<220>
<223> tripb

<400> 74

Gly Ser Ile Gln Gly Arg Ser Pro Gly Thr Glu Pro Pro Thr
1 5 10

<210> 75
<211> 6
<212> PRT
<213> Artificial

<220>
<223> tripb

<400> 75

Ala Leu Gln Thr Gly Ser
1 5

<210> 76
<211> 9
<212> PRT
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<220>
<223> pT7H6

<400> 76

Met Gly Ser His His His His His His
1 5

<210> 77
<211> 9
<212> PRT
<213> Artificial

<220>
<223> pT7CIIH6

<400> 77

Gly Ser Ile Glu Gly Arg Gly Glu Pro
1 5

<210> 78
<211> 2
<212> PRT
<213> Artificial

<220>
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<400> 78

Ile Val
1

<210> 79
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<212> PRT
<213> Artificial

<220>
<223> pT7CIIH6

<400> 79

Met Val Arg Ala
1

<210> 80
<211> 10
<212> PRT
<213> Artificial

<220>
<223> pT7CIIH6

<400> 80

Glu Gly Gly Ser His His His His His His
1 5 10

<210> 81
<211> 9
<212> PRT
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<220>
<223> pT7CIIH6

<400> 81

Met Gly Ser His His His His His His
1 5

<210> 82
<211> 10
<212> PRT
<213> Artificial

<220>
<223> pT7H6

<400> 82

Gly Ser Ile Glu Gly Arg Gly Glu Pro Pro
1 5 10

<210> 83
<211> 3
<212> PRT
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<220>
<223> pT7H6

<400> 83

Gln Thr Val
1

<210> 84
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<400> 84

Gly Ser Ile Gln Gly Arg Val Val Asn Thr
1 5 10

<210> 85
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<223> pT7H6

<400> 85

Gly Ile Val
1

<210> 86
<211> 9
<212> PRT
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<220>
<223> pT7H6

<400> 86

Gly Ser Ile Glu Gly Arg Ala Leu Gln
1 5

<210> 87
<211> 9
<212> PRT
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<220>
<223> pT7H6

<400> 87

Met Gly Ser His His His His His His
1 5

<210> 88
<211> 6
<212> PRT
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<220>
<223> pT7H6

<400> 88

Gly Ser Gln Ile Phe Val
1 5

<210> 89
<211> 4
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<220>
<223> pT7H6

<400> 89

Arg Gly Gly Ser
1

<210> 90
<211> 14
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<400> 90

Gly Ser Ile Gln Gly Arg Ser Pro Gly Thr Glu Pro Pro Thr
1 5 10

<210> 91
<211> 6
<212> PRT
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<220>
<223> pT7H6

<400> 91

Ala Leu Gln Thr Gly Ser
1 5

<210> 92
<211> 28
<212> DNA
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<220>
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<400> 92
gccctgcaga cgggatccta ataagctt 28

<210> 93
<211> 9
<212> PRT
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<220>
<223> pT7H6

<400> 93

Met Gly Ser His His His His His His
1 5

<210> 94
<211> 5
<212> PRT
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<220>
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<400> 94

Ser Gln Val Gln Leu
1 5

<210> 95
<211> 4
<212> PRT
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<220>
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<400> 95

Leu Asn Gly Ala
1

<210> 96
<211> 23
<212> PRT
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<220>
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<400> 96

Met Gly Ser His His His His His His Gly Ser Ile Gln Gly Arg Ser
1 5 10 15

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